

Community-acquired pneumonia

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ABSTRACT

INTRODUCTION: In the northern hemisphere about 12/1000 people a year (on average) contract pneumonia while living in the community, with most cases caused by *Streptococcus pneumoniae*. Mortality ranges from about 5–35% depending on severity of disease, with a worse prognosis in older people, men, and people with chronic diseases. **METHODS AND OUTCOMES:** We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of interventions to prevent community-acquired pneumonia? What are the effects of treatments for community-acquired pneumonia in outpatient settings, in people admitted to hospital, and in people receiving intensive care? We searched: Medline, Embase, The Cochrane Library, and other important databases up to June 2007 (BMJ Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). **RESULTS:** We found 21 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. **CONCLUSIONS:** In this systematic review we present information relating to the effectiveness and safety of the following interventions: antibiotics (oral, intravenous), different combinations, and prompt administration of antibiotics in intensive-care settings, early mobilisation, influenza vaccine, and pneumococcal vaccine.

QUESTIONS

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INTERVENTIONS

PREVENTION OF CAP

 Likely to be beneficial

Influenza vaccine (in elderly people)* 3

 Unlikely to be beneficial

Pneumococcal vaccine (for all-cause pneumonia and mortality in immunocompetent adults) 4

TREATMENTS (OUTPATIENTS)

 Likely to be beneficial

Antibiotics in outpatient settings (compared with no antibiotics)* 4

TREATMENTS (HOSPITAL)

 Likely to be beneficial

Antibiotics in hospital (compared with no antibiotics)* . . . 6

Early mobilisation (may reduce hospital stay compared with usual care)* 8

 Unlikely to be beneficial

Intravenous antibiotics in immunocompetent people in hospital without life-threatening illness (compared with oral antibiotics) 9

TREATMENTS (INTENSIVE CARE)

 Likely to be beneficial

Prompt administration of antibiotics in people admitted to intensive care with community-acquired pneumonia (improved outcomes compared with delayed antibiotic treatment)* 9

 Unknown effectiveness

Different combinations of antibiotics in intensive-care settings 10

Covered elsewhere in Clinical Evidence

Antivirals for influenza, in review on influenza.

Vaccines to prevent influenza in the elderly, in review on influenza.

To be covered in future updates

Shorter versus longer courses of antibiotics

Footnote

*Based on consensus.

Key points

- In the northern hemisphere about 12/1000 people a year (on average) contract pneumonia while living in the community, with most cases caused by *Streptococcus pneumoniae*.

People at greatest risk include those at the extremes of age, smokers, alcohol-dependent people, and people with lung or heart disease or immunosuppression.

Mortality ranges from about 5–35% depending on severity of disease, with a worse prognosis in older people, men, and people with chronic diseases.

- Deaths from influenza are usually caused by pneumonia. Influenza vaccine reduces the risk of clinical influenza, and may reduce the risk of pneumonia and mortality in elderly people.

Pneumococcal vaccine is unlikely to reduce all-cause pneumonia or mortality in immunocompetent adults, but may reduce pneumococcal pneumonia in this group.

- Antibiotics** lead to clinical cure in 80% or more of people with pneumonia being treated in the community or in hospital, although no one regimen has been shown to be superior to the others in either setting.

Early mobilisation may reduce hospital stay compared with usual care in people being treated with antibiotics.

Intravenous antibiotics have not been shown to improve clinical cure rates or survival compared with oral antibiotics in people treated in hospital for non-severe community-acquired pneumonia.

Continued treatment with oral amoxicillin after initial improvement with intravenous amoxicillin may not improve clinical cure rate compared with intravenous amoxicillin alone.

- Prompt administration** of antibiotics may improve survival compared with delayed treatment in people receiving intensive care for community-acquired pneumonia, although few studies have been done.

We don't know which is the **optimum antibiotic regimen** to use in these people.

DEFINITION	Community-acquired pneumonia is pneumonia contracted in the community rather than in hospital. It is defined by clinical symptoms (such as cough, sputum production, and pleuritic chest pain) and signs (such as fever, tachypnoea, and rales), with radiological confirmation.
INCIDENCE/ PREVALENCE	In the northern hemisphere, community-acquired pneumonia affects about 12/1000 people a year, particularly during winter, and in people at the extremes of age (annual incidence in people aged less than 1 year old: 30–50/1000; 15–45 years old: 1–5/1000; 60–70 years old: 10–20/1000; 71–85 years old: 50/1000). ^{[1] [2] [3] [4] [5] [6]}
AETIOLOGY/ RISK FACTORS	More than 100 micro-organisms have been implicated in community-acquired pneumonia, but most cases are caused by <i>Streptococcus pneumoniae</i> (see table 1, p 12). ^{[4] [5] [6] [7]} Case control study data suggest that smoking is probably an important risk factor. ^[8] One large cohort study conducted in Finland (4175 people aged at least 60 years) suggested that risk factors for pneumonia in older people included alcoholism (RR 9.0, 95% CI 5.1 to 16.2), bronchial asthma (RR 4.2, 95% CI 3.3 to 5.4), immunosuppression (RR 3.1, 95% CI 1.9 to 5.1), lung disease (RR 3.0, 95% CI 2.3 to 3.9), heart disease (RR 1.9, 95% CI 1.7 to 2.3), institutionalisation (RR 1.8, 95% CI 1.4 to 2.4), and increasing age (age at least 70 years v 60–69 years; RR 1.5, 95% CI 1.3 to 1.7). ^[9]
PROGNOSIS	Severity varies from mild to life-threatening illness within days of the onset of symptoms. A prospective cohort study (more than 14,000 people) found that old age was an extremely important factor in determining prognosis. ^[10] One systematic review of prognosis studies for community-acquired pneumonia (search date 1995, 33,148 people) found overall mortality to be 13.7%, ranging from 5.1% for ambulant people to 36.5% for people who required intensive care. ^[11] Prognostic factors significantly associated with mortality were: male sex (OR 1.3, 95% CI 1.2 to 1.4), absence of pleuritic chest pain (OR 2.00, 95% CI 1.25 to 3.30), hypothermia (OR 5.0, 95% CI 2.4 to 10.4), systolic hypotension (OR 4.8, 95% CI 2.8 to 8.3), tachypnoea (OR 2.9, 95% CI 1.7 to 4.9), diabetes mellitus (OR 1.3, 95% CI 1.1 to 1.5), neoplastic disease (OR 2.8, 95% CI 2.4 to 3.1), neurological disease (OR 4.6, 95% CI 2.3 to 8.9), bacteraemia (OR 2.8, 95% CI 2.3 to 3.6), leukopenia (OR 2.5, 95% CI 1.6 to 3.7), and multilobar radiographic pulmonary infiltrates (OR 3.1, 95% CI 1.9 to 5.1). ^[11]
AIMS OF INTERVENTION	Prevention: To prevent onset of pneumonia. Treatment: To cure infection clinically, to reduce mortality, to alleviate symptoms, to enable return to normal activities, and to prevent recurrence, while minimising adverse effects of treatments.
OUTCOMES	Prevention: Incidence of pneumonia; adverse effects of vaccination. Treatment: Clinical cure, variably defined but usually defined as return to pre-morbid health status or complete absence of symptoms or signs, such as fever, chills, cough, dyspnoea, or sputum production; treatment failure; improvement (relief of symptoms); admission to hospital or intensive care; duration of hospital stay (for treatment in people admitted to hospital); complications (empyema, endocarditis, lung abscess); death; quality of life; adverse effects of treatments.
METHODS	<i>BMJ Clinical Evidence</i> search and appraisal June 2007. The following databases were used to identify studies for this systematic review: Medline 1966 to June 2007, Embase 1980 to June 2007, and The Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials 2007, Issue 2. Additional searches were carried out using these websites: NHS Centre for Reviews and Dissemination (CRD) — for Database of Abstracts of Reviews of Effects

(DARE) and Health Technology Assessment (HTA), Turning Research into Practice (TRIP), and NICE. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as “open”, “open label”, or not blinded unless blinding was impossible. We also searched for cohort studies on prompt versus delayed antibiotic treatment: we included prospective and retrospective studies, with or without a control group, with a minimum of 50 people. We use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 13).

QUESTION	What are the effects of interventions to prevent community-acquired pneumonia?
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OPTION	INFLUENZA VACCINE
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Incidence of pneumonia

Compared with no vaccine Well-matched vaccines may be more effective at reducing the risk of pneumonia in elderly people residing in care homes, but not for elderly people living in the community (very low-quality evidence).

Mortality

Compared with no vaccine Well-matched vaccines may be more effective at reducing all-cause mortality in elderly people residing in care homes, and in the community (very low-quality evidence).

Hospital admission

Compared with no vaccine Well-matched vaccines may be more effective at reducing hospital admissions for pneumonia and influenza for people in long-term care facilities, and for elderly people living in the community (very low-quality evidence).

Note

We found no direct information about the effects of influenza vaccine in preventing community-acquired pneumonia.

For GRADE evaluation of interventions for community-acquired pneumonia, see table, p 13 .

Benefits:

We found one systematic review (search date 2004, 5 RCTs, 49 cohort studies, and 10 case control studies) comparing influenza vaccine versus no vaccine.^[12] None of the RCTs included in the review reported on pneumonia outcomes. In the absence of other evidence, we have reported results from the review of meta-analysis of cohort studies. The review did not report timescales for outcomes.

Pneumonia:

The review found that, in homes for elderly people, well-matched vaccines significantly reduced the risk of pneumonia compared with no vaccine (incidence of pneumonia: 8 cohort studies, 4482 people; vaccine efficiency [VE] 46%, 95% CI 30% to 58%; absolute numbers not reported).^[12] It found that, for elderly people living in the community, vaccines did not significantly reduce pneumonia compared with no vaccine (2 cohort studies, 18,090 people; RR 0.88, 95% CI 0.64 to 1.20).^[12]

Mortality:

The review found that, in homes for elderly people, well-matched vaccines significantly reduced risk of death from all causes compared with no vaccine (all-cause mortality: 1 cohort study, 305 people, VE 60%, 95% CI 23% to 79%; absolute numbers not reported).^[12] It found that, for elderly people living in the community, well-matched vaccines reduced death from all causes compared with no vaccine (7 cohort studies, 404,759 people, absolute data not reported; VE 42%, 95% CI 24% to 55%).

Hospital admission:

The review found that well-matched vaccines significantly reduced hospital admission for pneumonia and influenza for people in long-term care facilities compared with no vaccine (8 cohort studies, 2027 people, VE 45%, 95% CI 16% to 64%) and for elderly people living in the community (6 cohort studies, 727,776 people, VE 26%, 95% CI 12% to 38%).^[12] The review did not report admissions data for influenza and pneumonia separately.

Harms:

The review gave no information about adverse effects.^[12] We found no RCTs.

Comment: **Clinical guide:**
A reduction in rates of influenza does not necessarily imply a reduction in rates of pneumonia. However, in people with influenza, death is usually caused by pneumonia. Therefore, interventions that reduce influenza mortality exert their effects by reducing pneumonia rates.

OPTION	PNEUMOCOCCAL VACCINE
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Incidence of pneumonia

Compared with no vaccine Pneumococcal vaccine seems no more effective at reducing all-cause pneumonia or definitive pneumonia in immunocompetent adults ([moderate-quality evidence](#)).

Mortality

Compared with no vaccine Pneumococcal vaccine seems no more effective at reducing all-cause mortality in immunocompetent adults ([moderate-quality evidence](#)).

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits: We found one systematic review (search date 2003, 14 RCTs, more than 75,000 adults aged at least 16 years), which compared pneumococcal vaccination versus no vaccination.^[13] Studies were done in a variety of countries between 1937 and 1995. The review excluded studies of people who were HIV positive. It found no significant difference between vaccination and no vaccination in all-cause pneumonia or all-cause mortality, but these results should be interpreted with caution, as there was significant heterogeneity found for both meta-analyses (see comment) (all-cause pneumonia: 14 RCTs, OR 0.77, 95% CI 0.58 to 1.02; all-cause mortality: 11 RCT, OR 0.90, 95% CI 0.76 to 1.07).^[13] It found that pneumococcal vaccine significantly reduced definitive pneumococcal pneumonia compared with no vaccination — but again, significant heterogeneity was found, and results were sensitive to the removal of one older, poorer-quality RCT (see comment; 8 RCTs: 0.13% with vaccination v 0.54% with no vaccination; OR 0.28, 95% CI 0.15 to 0.52).^[13]

Harms: The systematic review found few RCTs that gave information on adverse effects.^[13] One RCT in the review found that pneumococcal vaccination was associated with erythema and induration compared with no vaccination. Another RCT in the review found that pneumococcal vaccination increased sore arm, swollen arm, and fever, compared with no vaccination.

Comment: Several of the RCTs included in the systematic review reported incomplete data, and clarification of data was not possible because of the age of some RCTs.^[13] In the review, the heterogeneity between studies for all-cause mortality and definitive pneumococcal pneumonia seemed partly explained by inclusion of one older, poorer-quality RCT. Omitting this RCT from the analysis did not change the results for all-cause mortality (10 RCTs: OR 0.95, 95% CI 0.90 to 1.01) or definitive pneumococcal pneumonia (13 RCTs: 2.8% with vaccination v 3.9% with no vaccination; OR 0.84, 95% CI 0.65 to 1.08). The systematic review also examined non-randomised studies. Pooling of five case control studies found that vaccination significantly reduced invasive pneumococcal disease (OR 0.47, 95% CI 0.37 to 0.59). The fact that older studies examined vaccines with different valencies also may explain some of the heterogeneity. The more recent studies in the review were consistent in providing no evidence of efficacy of the vaccine against pneumonia.

QUESTION	What are the effects of treatments for community-acquired pneumonia in outpatient settings?
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OPTION	ANTIBIOTICS
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Clinical cure

Clarithromycin compared with erythromycin We don't know whether clarithromycin is more effective at increasing clinical success (defined as improving or clearing signs and symptoms) in ambulatory outpatients with community-acquired pneumonia ([low-quality evidence](#)).

Sparfloxacin compared with clarithromycin Sparfloxacin and clarithromycin seem equally effective at increasing rates of clinical success (defined as disappearance of most or all signs and symptoms as assessed by chest radiography) at 10 days ([moderate-quality evidence](#)).

Azithromycin compared with levofloxacin Azithromycin and levofloxacin seem equally effective at increasing clinical success rates (defined as disappearance of most or all signs and symptoms as assessed by chest radiography) at 10 days ([moderate-quality evidence](#)).

Azithromycin compared with clarithromycin Azithromycin and clarithromycin seem equally effective at increasing clinical cure rates (defined as improvement or resolution of signs and symptoms such that no more antibiotics are needed, and chest radiograph no worse) at 14–21 days ([moderate-quality evidence](#)).

Note

We found no direct information about whether antibiotics are better than active treatment or no active treatment. There is consensus that antibiotics are beneficial for community-acquired pneumonia.

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits:**Antibiotics versus placebo or no treatment:**

We found no RCTs (see comment).

Different antibiotic regimens versus each other:

We found one systematic review (search date 2003, 3 RCTs) ^[14] comparing different antibiotic treatments for community-acquired pneumonia in ambulatory outpatients above 12 years of age, and three subsequent RCTs. ^[15] ^[16] ^[17] The systematic review had stringent inclusion and exclusion criteria, and excluded studies if inpatient and outpatient results were not reported separately. ^[14] Most of these RCTs were designed to show equivalence between treatments rather than superiority of one antibiotic over another.

Clarithromycin versus erythromycin:

The review found no significant difference between clarithromycin and erythromycin in rates of clinical success (2 RCTs, 280 people; clinical success defined as cure or improvement: OR 2.27, 95% CI 0.66 to 7.80). One of these RCTs defined “cure” as complete resolution of all signs and symptoms and “improvement” as partial resolution of signs and symptoms; in the second RCT, the definitions of “cure” and “improvement” were not clear. Clinical success was at least 90% for all interventions in both RCTs. ^[14]

Sparfloxacin versus clarithromycin:

The third RCT identified by the review found no significant difference in clinical success rates 10 days after treatment between sparfloxacin and clarithromycin (342 people, intention-to-treat [ITT] analysis; AR: 80% with sparfloxacin v 83% with clarithromycin; difference reported as not significant; P value and CIs not reported). ^[17] This RCT defined “cure” as disappearance of all clinical signs and symptoms, and “improvement” as disappearance of most clinical signs and symptoms; both improvement and cure required chest radiograph signs to be resolved, improved, or stable.

Telithromycin versus clarithromycin:

The first additional RCT compared oral telithromycin (800 mg daily for 10 days) versus oral clarithromycin (500 mg daily for 10 days), but was excluded from this review as it had less than 80% follow-up. ^[15]

Azithromycin versus levofloxacin:

The second subsequent RCT (non-inferiority design, 427 people, 394 [92%] in the ITT analysis; 363 [85%] in per protocol analysis) found no significant difference in clinical cure rates between azithromycin (single-dose 2.0 g microsphere formulation) and levofloxacin (500 mg daily for 7 days) at 14–21 days (ITT analysis: 165/195 [85%] with azithromycin v 179/199 [89%] with levofloxacin; CI not calculated; per protocol analysis: 156/174 [90%] with azithromycin v 177/189 [94%] with levofloxacin; ARI +4.0, 95% CI –9.7 to +1.7; P values not reported; differences reported as not significant). ^[16] Clinical cure was defined as improvement or resolution of signs and symptoms such that no more antibiotics were thought to be needed.

Azithromycin versus clarithromycin:

The third subsequent RCT (501 people, 499 [more than 99%] in the ITT analysis; 411 [82%] in the clinical per protocol analysis) found no significant difference in clinical cure rates between azithromycin (single-dose 2.0 g microsphere formulation) and extended-release clarithromycin (1 g daily for 7 days) at 14–21 days (ITT analysis: 215/247 [87%] with azithromycin v 218/252 [87%] with azithromycin; reported as not significant; clinical per protocol analysis: 187/202 [93%] with azithromycin v 198/209 [95%] with azithromycin; P and CI values not reported). ^[17] Clinical cure was defined as improvement or resolution of signs and symptoms such that no more antibiotics were thought needed, and chest radiograph no worse.

Harms:

Antibiotics can cause allergic reactions (including anaphylaxis), rash, gastrointestinal intolerance (nausea, vomiting, and diarrhoea), vaginal or oral candidiasis, and *Clostridium difficile* diarrhoea (including pseudomembranous colitis), and lead to the development of antimicrobial-resistant bacteria. The frequency of adverse effects and type of antimicrobial resistance varies with the antibiotic used.

Antibiotics versus placebo or no treatment:

We found no RCTs.

Clarithromycin versus erythromycin:

The systematic review found that erythromycin significantly increased adverse effects compared with clarithromycin in both included RCTs, but there was no significant difference between treatments in withdrawals caused by adverse effects (first RCT, AR for adverse effects: 59% with erythromycin v 31% with clarithromycin; P less than 0.001; second RCT, no data reported; no absolute data reported for withdrawal caused by adverse effects).^[14] Most adverse effects were gastrointestinal.

Sparfloxacin and clarithromycin:

The review found a similar incidence of adverse effects with sparfloxacin and clarithromycin (1 RCT, 342 people; AR: 56% with sparfloxacin v 65% with clarithromycin; significance not reported).

Telithromycin versus clarithromycin:

The first subsequent RCT found that telithromycin increased adverse effects compared with clarithromycin, but the statistical significance of this finding was not reported (126/221 [57%] with telithromycin v 109/222 [49%] with clarithromycin).^[15] The most common adverse effects were gastrointestinal.

US Food and Drug Administration (FDA) safety alert for Ketek (telithromycin):

The FDA issued a safety alert about the risk of serious liver injury and liver failure from the use of Ketek (telithromycin). The drug has been associated with rare cases of serious liver injury and liver failure, with four reported deaths and one liver transplant after the administration of the drug. The FDA determined that additional warnings are required, and the manufacturer is revising the drug labelling to address this safety concern. The FDA is advising that people taking Ketek and their doctors to be on the alert for signs and symptoms of liver problems. People experiencing such signs or symptoms should discontinue Ketek (telithromycin) and seek medical evaluation, which may include tests for liver function.^[18]

Azithromycin versus levofloxacin:

The second subsequent RCT found that slightly more people in the azithromycin group reported at least one adverse reaction than in the levofloxacin group (84/211 [40%] with azithromycin v 65/212 [31%] with levofloxacin).^[16] Adverse events were mostly gastrointestinal.

Azithromycin versus clarithromycin:

In the third subsequent RCT, a similar proportion of adverse events occurred in both groups, most of which were gastrointestinal (65/246 [26%] with azithromycin v 62/252 [25%] with clarithromycin; significance not reported).^[17]

Comment:

There is consensus that antibiotics are beneficial for community-acquired pneumonia, and placebo-controlled trials are unlikely to be considered ethical.

QUESTION

What are the effects of treatments for community-acquired pneumonia in people admitted to hospital?

OPTION**ANTIBIOTICS****Clinical cure**

Intravenous amoxicillin plus oral amoxicillin compared with intravenous amoxicillin plus placebo Continuing treatment with oral amoxicillin seems no more effective than placebo at increasing clinical cure rates at 10 days after initial treatment with intravenous amoxicillin in people admitted to hospital with mild to moderate community-acquired pneumonia (moderate-quality evidence).

Atypical coverage regimens compared with non-atypical coverage regimens Antibiotic regimens including antibiotics active against atypical pathogens (predominantly quinolones and macrolides) and regimens without atypical coverage (predominantly beta-lactams and cephalosporins) seem equally effective at reducing clinical failure rates (moderate-quality evidence).

Penicillin compared with cephalosporins Penicillin and cephalosporins seem equally effective at increasing clinical cure rates in the long term (moderate-quality evidence).

Quinolones compared with co-amoxiclav Moxifloxacin seems more effective at increasing clinical cure rates at 5–7 days after treatment (moderate-quality evidence).

Mortality

Antibiotic regimens containing antibiotics active against atypical pathogens (predominantly quinolones and macrolides) and regimens without atypical coverage (predominantly beta-lactams and cephalosporins) seem equally effective at reducing mortality (moderate-quality evidence).

Note

We found no direct information about whether antibiotics are better than active treatment or no active treatment. There is consensus that antibiotics are beneficial for community-acquired pneumonia.

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits:**Antibiotics versus placebo or no treatment:**

We found no systematic review or RCTs (see comment).

Intravenous amoxicillin plus oral amoxicillin versus intravenous amoxicillin plus placebo:

We found one RCT.^[19] People admitted to hospital with mild to moderate community-acquired pneumonia who improved after 3 days of treatment with intravenous amoxicillin were randomised (121 people) to oral amoxicillin 750 mg three times daily or placebo for 5 days. The RCT carried out an intention-to-treat analysis (all randomised people who received at least one dose of study drug). The RCT found no significant difference in clinical cure rate at 10 days after initial treatment with intravenous amoxicillin between continued treatment with oral amoxicillin and placebo (56/63 [88.8%] with amoxicillin v 50/56 [89.2%] with placebo; ARR +0.4%, 95% CI -11% to +12%). There was also no significant difference between groups in clinical cure rate at 28 days (49/63 [78%] with amoxicillin v 47/56 [84%] with placebo: ARR +6%, 95% CI -8% to +20%).

Atypical coverage regimens versus non-atypical coverage regimens:

We found one systematic review (search date 2005, 24 RCTs, 5015 people) comparing regimens including antibiotics active against atypical pathogens versus regimens without atypical coverage.^[20] The review found no significant difference in mortality between atypical regimens and non-atypical regimens (93/2622 [3.5%] with atypical v 67/2224 [3.0%] with non-atypical; RR 1.13, 95% CI 0.82 to 1.54). It found no significant difference in mortality between either quinolones or macrolides and non-atypical regimens (quinolone, 19 RCTs: RR 0.98, 95% CI 0.69 to 1.41; macrolide, 4 RCTs: RR 1.25, 95% CI 0.52 to 3.01). In the review the average mortality in the included trials, 3.7%, is substantially lower than the 10%^[21] usually reported for people hospitalised for community-acquired pneumonia.^[20] Although overall analysis suggested that atypical coverage regimens significantly increased bacteriological eradication compared with non-atypical coverage regimens (RR 0.73, 95% CI 0.59 to 0.91), this significant difference was not retained if only the high-quality studies were analysed (RR 0.89, 95% CI 0.60 to 1.30). The review found no significant difference in clinical failure between the atypical and non-atypical regimen (542/2538 [21.4%] with atypical v 447/2144 [20.8%] with non-atypical; RR 0.92, 95% CI 0.82 to 1.03). The systematic review compared regimens including antibiotics active against atypical pathogens (macrolide, fluoroquinolone, tetracycline, doxycycline, or chloramphenicol) versus regimens without atypical coverage.^[20] Atypical regimens included a quinolone (19 RCTs) or a macrolide (4 RCTs), and one RCT pooled results for people taking either quinolone or a macrolide. In all but two RCTs, the atypical arm was given as a monotherapy. The drugs were given orally in all but six studies, and most of these six studies switched to oral administration within a few days. The non-atypical treatments included beta lactam (8 RCTs), beta lactam plus beta lactamase inhibitor (3 RCTs), cephalosporin (8 RCTs), carbapenems (2 RCTs), and penicillin (1 RCT). Most of the RCTs included in the review were small, and were designed to show equivalence between treatments rather than superiority of one antibiotic over another. Although detection of penicillin-resistant and multidrug-resistant *Streptococcus pneumoniae* is commonly reported, it is difficult to enrol people with this infection in randomised studies.

Penicillin versus cephalosporins:

We found no systematic review. We found several RCTs that were too small, too old, or both, to be reliable, given the changing sensitivity of organisms to antibiotics. One RCT (378 people) compared penicillin (iv co-amoxiclav [amoxicillin plus clavulanic acid] followed by oral co-amoxiclav) versus cephalosporins (iv ceftriaxone followed by im ceftriaxone).^[22] People in both groups also received intravenous erythromycin as decided by their physician (17/184 [9%] people taking co-amoxiclav and 25/194 [13%] people taking ceftriaxone). The RCT found no significant difference in clinical cure at long-term follow-up, which was not specified (136/184 [73.9%] with co-amoxiclav v 144/194 [74.2%] with ceftriaxone; RR 0.99, 95% CI 0.88 to 1.12).

Quinolones versus co-amoxiclav:

We found no systematic review. We found one multicentre RCT (628 people) comparing a quinolone (moxifloxacin 400 mg once daily, iv followed by oral) versus co-amoxiclav (1.2 g iv followed by 625 mg orally 3 times daily with or without clarithromycin for 7–14 days).^[23] It found that moxifloxacin significantly increased the clinical cure rate at 5–7 days after treatment compared with co-amoxiclav (225/241 [93%] with moxifloxacin v 204/239 [85%] with co-amoxiclav; P = 0.004).^[23]

Harms:

See harms of antibiotics in outpatient settings, p 4.

Antibiotics versus placebo or no treatment:

We found no RCTs.

Intravenous amoxicillin plus oral amoxicillin versus intravenous amoxicillin plus placebo:

The RCT found no significant difference in the proportion of people reporting mild adverse effects during or at the end of treatment between the oral amoxicillin group and the placebo group, although the proportion of people reporting an adverse effect was larger with oral amoxicillin (13/63 [21%] with amoxicillin v 6/56 [11%] with placebo; $P = 0.1$).^[19] The RCT gave no further information on the adverse effects reported.

Atypical coverage regimens versus non-atypical coverage regimens:

The systematic review found no significant difference in overall adverse events between atypical and non-atypical coverage regimens (22 RCTs, 4261 people: 450/2131 [21%] with atypical v 435/2130 [20%] with non-atypical; RR 1.02, 95% CI 0.91 to 1.13).^[20]

Penicillin versus cephalosporins:

The RCT gave no information on adverse effects.^[22]

Quinolones versus co-amoxiclav:

The RCT found the same rate of overall adverse effects (primarily nausea and diarrhoea) between quinolones (moxifloxacin) and co-amoxiclav (39% in both groups; CI not reported).^[23]

Drug safety alert:

A drug safety alert has been issued on serious hepatic and bullous skin reactions associated with moxifloxacin (http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON014103&RevisionSelectionMethod=Latest).

Comment:

There is consensus that antibiotics are beneficial for community-acquired pneumonia and placebo-controlled trials may be considered unethical.

OPTION**EARLY MOBILISATION****Duration of hospital stay**

Early mobilisation alone compared with usual care Early mobilisation alone may be more effective at reducing the mean duration of hospital stay (*moderate-quality evidence*).

Clinical cure

Different early mobilisation regimens compared with each other (early mobilisation, early mobilisation plus encouragement to sit up 10 times a day and take 20 deep breaths, early mobilisation plus encouragement to sit up 10 times a day plus bottle-blowing physiotherapy) We don't know whether one early-mobilisation regimen is more effective than the others at reducing duration of fever in people in hospital with community-acquired pneumonia (*low-quality evidence*).

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits:**Early mobilisation alone versus usual care:**

We found no systematic review. We found one RCT.^[24] The RCT (459 people) compared early mobilisation alone versus usual care.^[24] The RCT found no significant difference between early mobilisation and usual care in length of hospital stay, although mean duration of hospital stay was shorter with early mobilisation compared with usual care (5.8 days with early mobilisation v 6.9 days with usual care; absolute difference 1.1 days, 95% CI 0 days to 2.2 days).

Different early-mobilisation regimens:

We found no systematic review. We found one RCT.^[25] The RCT (145 people in hospital with community-acquired pneumonia) compared three interventions: early mobilisation alone; early mobilisation plus encouragement to sit up 10 times a day and take 20 deep breaths; and early mobilisation plus encouragement to sit up 10 times a day and blow bubbles through a plastic tube for 20 breaths into a bottle containing 10 cm of water (*bottle blowing*).^[25] People concurrently received benzylpenicillin or phenoxymethylpenicillin plus usual medical care independently of the study interventions. The RCT found that encouragement to sit up and do bottle blowing plus early mobilisation significantly reduced mean hospital stay compared with early mobilisation alone (3.9 days with bottle blowing plus early mobilisation plus encouragement v 5.3 days with early mobilisation alone; $P = 0.01$). It found no significant difference among groups in duration of fever (2.3 days with early mobilisation alone v 1.7 days with encouragement to take deep breaths v 1.6 days with bottle blowing; $P = 0.28$ for all groups v each other).^[25]

Harms:

The RCTs gave no information on adverse effects.^{[24] [25]}

Comment: None.

OPTION ORAL VERSUS INTRAVENOUS ANTIBIOTICS

Clinical cure

Oral compared with intravenous antibiotics Oral and intravenous antibiotics are equally effective at increasing clinical success rates in people admitted to hospital with non-life-threatening community-acquired pneumonia ([high-quality evidence](#)).

Mortality

Oral compared with intravenous antibiotics Oral and intravenous antibiotics are equally effective at reducing mortality in people admitted to hospital with non-life-threatening community-acquired pneumonia (high-quality evidence).

Duration of hospital stay

Oral compared with intravenous antibiotics We don't know whether oral antibiotics are more effective than intravenous antibiotics at reducing the mean duration of hospital stay in people admitted to hospital with non-life-threatening community-acquired pneumonia ([low-quality evidence](#)).

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits:

Oral versus intravenous antibiotics:

We found one systematic review (search date 2003, 7 RCTs, 1366 people) comparing oral (various) versus intravenous (various) antibiotics in people admitted to hospital with non-life-threatening community-acquired pneumonia. ^[26] The systematic review found no significant difference between oral and intravenous antibiotics in clinical success or mortality (clinical success: 261/290 [90%] with oral v 220/255 [86%] with iv; RR 1.07, 95% CI 0.98 to 1.16; mortality: 8/292 [3%] with oral v 14/299 [5%] with iv; RR 0.61, 95% CI 0.26 to 1.4). ^[26] The review found that mean length of hospital stay was shorter with oral compared with intravenous antibiotics (6.1 days with oral v 7.8 days with iv; significance not assessed).

Harms:

The systematic review gave no information on adverse effects. ^[26]

Comment:

Clinical guide:

Intravenous antibiotics are used in people who cannot take oral medication because of severe nausea or vomiting.

QUESTION What are the effects of treatments in people with community-acquired pneumonia receiving intensive care?

OPTION PROMPT VERSUS DELAYED ANTIBIOTIC TREATMENT

Mortality

Prompt compared with delayed (more than 8 hours or more after admission) antibiotic treatment Antibiotics given within 8 hours of admission to hospital may be more effective at lowering mortality at 30 days in severely ill people with community-acquired pneumonia ([very low-quality evidence](#)). We found no clinically important results about prompt compared with delayed antibiotic treatment.

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits:

Prompt versus delayed antibiotic treatment:

We found no systematic review or RCTs (see comment). One large multicentre retrospective cohort study (medical records of at least 14,000 people aged 65 years and older admitted to acute [emergency] care hospitals in the USA who were severely ill with community-acquired pneumonia) found that antibiotics given within 8 hours of admission to hospital were associated with a significantly lower 30-day mortality compared with antibiotics given at least 8 hours after admission (OR 0.85, 95% CI 0.75 to 0.96). ^[27] The study did not specify whether oral or intravenous antibiotics were given.

Harms:

Prompt versus delayed antibiotic treatment:

We found no RCTs. The retrospective study gave no information on adverse effects. ^[27]

Comment:

It may be regarded as unethical to perform an RCT of delayed antibiotic treatment.

OPTION	DIFFERENT COMBINATIONS OF ANTIBIOTICS
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We found no clinically important results about one combination of antibiotics compared with another in intensive care units in people with community-acquired pneumonia.

For GRADE evaluation of interventions for community-acquired pneumonia, see [table, p 13](#).

Benefits:	We found no systematic review or RCTs that compared one combination of antibiotics versus another in intensive care units (see comment).
Harms:	We found no RCTs.
Comment:	Clinical guide: Use of a combination of antibiotics is regarded as current best practice for ventilator-related pneumonia. Choice of antibiotics varies, depending on local guidelines.

GLOSSARY

Bottle Blowing aims to help push air into the lungs to open up inflamed alveoli so that oxygen can pass into the bloodstream. Bottle blowing requires a person to sit up in bed and take deep breaths, which assist the lungs, and may encourage the person to cough and bring up sputum, thereby helping the lungs to recover.

Vaccine efficiency (VE) $VE = 1$ minus the relative risk (RR), that is, the relative risk reduction (RRR) expressed as a percentage. For example, if $RR = 0.4$, $VE = 60\%$, that is $(1 - 0.4 = 0.6) \times 100$.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Antibiotics in hospital Categorisation changed from Beneficial by consensus to Likely to be beneficial by consensus for antibiotics compared with no antibiotics; insufficient evidence to support a categorisation of Beneficial by consensus; all evidence available is equivalence testing of different antibiotic regimens compared with each other. One RCT added assessing the effects of continued treatment with oral amoxicillin after improvement with treatment using intravenous amoxicillin for 3 days.^[19] The RCT found no significant difference in clinical cure rate at 10 days between placebo and continued treatment with oral amoxicillin for 5 days.

Antibiotics in outpatient settings Categorisation changed from Beneficial by consensus to Likely to be beneficial by consensus for antibiotics compared with no antibiotics; insufficient evidence to support a categorisation of Beneficial by consensus; all evidence available is equivalence testing of different antibiotics compared with each other.

Early mobilisation (reduced hospital stay compared with usual care) Evidence re-assessed; categorisation changed to Likely to be beneficial by consensus; insufficient good-quality evidence to support a categorisation of Likely to be beneficial based on the RCT evidence we found alone.

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TABLE 1 Causes of community-acquired pneumonia (see text).

	USA (% of participants)*	UK (% of participants) [†]	Susceptibility (laboratory results) [‡]
<i>Streptococcus pneumoniae</i>	20–60	60–75	25% penicillin-resistant, sensitive to quinolones
<i>Haemophilus influenzae</i>	3–10	4–5	30% ampicillin-resistant, sensitive to cephalosporins or co-amoxiclav
<i>Staphylococcus aureus</i>	3–5	1–5	Methicillin-resistant <i>S aureus</i> rare as cause of community-acquired pneumonia
<i>Chlamydia pneumoniae</i>	4–6	ND	Sensitive to macrolides, tetracyclines, quinolones
<i>Mycoplasma pneumoniae</i>	1–6	5–18	Sensitive to macrolides, tetracyclines, quinolones
<i>Legionella pneumophila</i>	2–8	2–5	Sensitive to macrolides, tetracyclines, quinolones
Gram-negative bacilli	3–10	Rare	
Aspiration	6–10	ND	
Viruses	2–15	8–16	

*Pooled data from 15 published reports from North America; ^[7] †data from British Thoracic Society; ^[7] ‡susceptibility data from recent studies.
 ND, no data.

TABLE GRADE evaluation of interventions for community-acquired pneumonia

Important outcomes		Incidence of pneumonia, clinical cure, complications, admission to hospital or intensive care, mortality, duration of hospital stay, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of interventions to prevent community-acquired pneumonia?									
10 studies (22,572) ^[12]	Incidence of pneumonia	Influenza vaccine v no vaccine	2	−1	0	0	0	Very low quality	Quality point deducted for incomplete reporting of results
8 studies (405,064) ^[12]	Mortality	Influenza vaccine v no vaccine	2	−1	0	0	0	Very low quality	Quality point deducted for incomplete reporting of results
14 studies (729,803) ^[12]	Hospital admission	Influenza vaccine v no vaccine	2	−1	0	0	0	Very low quality	Quality point deducted for incomplete reporting of results
13 (at least 200 people) ^[13]	Incidence of pneumonia	Pneumococcal vaccine v no vaccine	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
10 (at least 200 people) ^[13]	Mortality	Pneumococcal vaccine v no vaccine	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatments for community-acquired pneumonia in outpatient settings?									
2 (280) ^[14]	Clinical cure	Clarithromycin v erythromycin	4	−1	0	−1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about definition of outcome
1 (342) ^[17]	Clinical cure	Sparfloxacin v clarithromycin	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (394) ^[16]	Clinical cure	Azithromycin v levofloxacin	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (499) ^[17]	Clinical cure	Azithromycin v clarithromycin	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
What are the effects of treatments for community-acquired pneumonia in people admitted to hospital?									
1 (119) ^[19]	Clinical cure	Intravenous amoxicillin plus oral amoxicillin v intravenous amoxicillin plus placebo	4	−1	0	0	0	Moderate	Quality point deducted for sparse data
At least 1 RCT (4682) ^[20]	Clinical cure	Atypical coverage regimens v non-atypical coverage regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
At least 1 RCT (4846) ^[20]	Mortality	Atypical coverage regimens v non-atypical coverage regimens	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (378) ^[22]	Clinical cure	Penicillin v cephalosporins	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of co-intervention
1 (480) ^[23]	Clinical cure	Quinolones v co-amoxiclav	4	0	0	−1	0	Moderate	Directness point deducted for inclusion of co-intervention
1 (459) ^[24]	Duration of hospital stay	Early mobilisation alone v usual care	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of data

Incidence of pneumonia, clinical cure, complications, admission to hospital or intensive care, mortality, duration of hospital stay, adverse effects									
Important outcomes	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
Number of studies (participants)									
1 (145) ^[25]	Clinical cure	Different early mobilisation regimens	4	−2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
At least 1 RCT (545) ^[26]	Clinical cure	Oral v intravenous antibiotics	4	0	0	0	0	High	
At least 1 RCT (595) ^[26]	Mortality	Oral v intravenous antibiotics	4	0	0	0	0	High	
At least 1 (unclear) ^[26]	Duration of hospital stay	Oral v intravenous antibiotics	4	−2	0	0	0	Low	Quality points deducted for no direct statistical comparison between groups and incomplete reporting of data
What are the effects of treatments in people with community-acquired pneumonia receiving intensive care?									
1 study (14,000) ^[27]	Mortality	Prompt v delayed antibiotic treatment	2	−1	0	−1	0	Very low quality	Quality point deducted for incomplete reporting of results. Directness point deducted for uncertainty about method of administration
Type of evidence: 4 = RCT; 2 = Observational Consistency: similarity of results across studies Directness: generalisability of population or outcomes Effect size: based on relative risk or odds ratio									